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Docket No.: 515-4183

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
Maurizio Valeri et al) Group Art Unit:
) Examiner:
)
Serial No.: 09/463,586)
)
Filed: April 24, 2000)

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For: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

New York, NY 10036
May 7, 2002

Commissioner for Patents
Washington D.C. 20231

LETTER

Sir:

Attached are three copies of an Appeal Brief in compliance with 37 CFR§1.192.

Also attached is a check for $320.00 in payment of the Appeal Fee.

Respectfully submitted,

James V. Costigan
Registration No. 25,559

MAILING ADDRESS:
Hedman & Costigan, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

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13/Appeal Brief (3) clm 5-1-02

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New York, NY 10036
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APPEAL BRIEF

Sir:

This is an appeal from the final rejection of all rejected claims by the Primary Examiner.

(1) Real Party in Interest

The real party in interest is Menarini International Operations Luxembourg S.A.

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 1-8 and 13-18 have been finally rejected. Claims 9-12 have been finally objected to as being dependent on a rejected base claim, but indicated to be allowable if rewritten to include all the limitations of the base claims and any intervening claims.

(4) Status of Amendments

No Amendment was filed in response to the final rejection.

(5) Summary of Invention

The present invention refers to pharmaceutical compositions containing Vitamin D and a calcium salt, the process for their preparation, and their use in the treatment of pathological forms involving loss of bone tissue in the elderly, such as osteoporosis, as well as the prevention of illnesses linked to calcium metabolism in the elderly, such as those leading to fractures of the proximal femur or other non-vertebral fractures.

(6) Issues

Do the teachings of Silver, EP 588 539 A1, make Claims 1-7 unpatentable under 35 U.S.C. §102?

Do the teachings of FR-A-2 724 844 make claims 1-8 and 13-18 unpatentable under 35 U.S.C. §103?

(7) Grouping of Claims

All separate grounds for rejection are to be considered separately. Claims 1-7 are to be considered together, Claims 1-8 and 13-18 are to be considered together.

(8) Argument

Claims 1-7 were rejected under 35 U.S.C. 102(b) as being anticipated by Silver, EP 588 539A (hereinafter Silver). This rejection is in error for the following reasons.

The present invention is a pharmaceutical composition containing as active ingredients both Vitamin D and a calcium salt (see Claim 1 at lines 1 and 2). Silver is limited to a disclosure of a pharmaceutical composition which comprises at least ingredients (a), (b) and (c) and optionally the component (d) (see Claim 1, page 5 and the specification page 3, line 25) which is selected from lactose, sorbitol and calcium phosphate (see Claim 6, page 5). More importantly, nowhere does Silver disclose the use of calcium salt as an active ingredient. The only use of a calcium salt according to Silver is as an optional excipient or carrier.

Furthermore, the Calcium phosphate disclosed in Silver is

clearly an excipient added in order to make a solid composition that is specifically defined in Claim 1 as "an amount sufficient to impart the characteristics of a solid to the composition." The Examiner, in the Office Action dated June 19, 2001, points out that Silver teaches the use of polyethylene glycol as a stabilizer, however, like the choice of calcium phosphate, this is optional. Moreover, neither the use of polyethylene glycol, nor the use of 1-2 g of calcium salt to 500-1000 IU vitamin D, is disclosed in any of Silver's reported examples.

As taught by Silver, the ratio of Vitamin D to calcium salt only relates to its properties as an excipient, and does not teach the use of this material for its therapeutic effects as in the present claimed application.

The Examiner stated "the reference does not disclose the amounts of Vitamin D and calcium salt in the same manner claimed by the Applicant, and therefore, there is no means for comparison." Silver discloses a composition of Vitamin D_2 and Vitamin D_3 derivatives, an antioxidant, and a solid pharmaceutical excipient or carrier. Silver does not disclose calcium in combination with Vitamin D. In Silver, calcium phosphate may be used as an excipient, but lactose or sorbitol may alternatively be used. Furthermore, in Silver a lubricant from the group consisting of calcium stearate or magnesium stearate may be added. However, a lubricant is not required. Calcium need not be present in Silver, even though it represents the largest active ingredient in the present application. Further, no therapeutic use of calcium is even hinted at in Silver.

Other significant differences are found between Silver and the present application. Unlike Silver, the present invention includes liquid paraffin or silicone oil. Unlike Silver, the present application does not require any antioxidant. Unlike Silver, there are required binders of propylene glycol or polyethylene glycol, liquid paraffin or silicone oil. There is nothing of record that would suggest the addition of these binders. In short, Silver does not

disclose a pharmaceutical formulation of calcium and Vitamin D in the specific ratio claimed (high quantity of calcium, low quantity of Vitamin D) with specific binders, nor could the same be anticipated.

Furthermore, the claimed invention in Silver relates to derivatives of Vitamin D. More particularly, Silver claims specific mono-, di- or tri-hydroxy derivatives of Vitamin D. In contrast, the present application refers to Vitamin D itself. These derivatives are wholly different products from the vitamin itself and cannot be considered vitamins per se from a chemical or pharmaceutical standpoint. Therefore, based on the reasons set forth above and the differing composition of vitamins and their derivatives, the present claimed invention is not anticipated by Silver.

Claims 1-8 and 13-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over FR-A-2 724 844 (hereinafter FR '844). This rejection is in error for the following reasons.

It should be noted that the FR '844 patent refers to a pharmaceutical composition which must be prepared in a "humid environment" (see claim 4, page 11). However, because of the specifically chosen binders of the present invention, the application can be prepared without using water. Further, it is well known in the art that the use of a humid process of preparation can leave traces of humidity in the granules, which may result in a degradation of the Vitamin D, which undergoes spontaneous oxidation.

The present invention requires the use of calcium phosphate salts and their analogues, i.e. compounds that have a high content of calcium but are insoluble. The calcium salts used in the prior art normally underwent a granulation process to avoid poor flow characteristics. This made them unsuitable for processing using ordinary high output machines. However, when used in suspensions, these granules increased the rate of sedimentation causing a "sand effect", thereby decreasing the uniformity of the distribution of the active ingredients within the product. In order to make pharmaceutical compositions for oral use that do not present a

"sand effect" it is necessary to identify the exact additives that show acceptable texture, and at the same time allow for an industrial preparation of the composition. Therefore, it was necessary to utilize binders that would be effective in a dry environment, with high concentrations of an insoluble calcium salt such as calcium phosphates. These conditions and binders are not disclosed in FR '844.

As stated by the Examiner, in the Office Action dated June 19, 2001, "FR '844 does not teach all of the specific additives claimed by the applicant. Additionally, the reference does not disclose the amounts of Vitamin D and calcium salt in the same manner claimed by the applicant." The binding agents of the present invention, propylene glycol, polyethylene glycol, liquid paraffin or silicone oil are not disclosed in FR '844. More particularly with respect to FR '844, the formulation contains 500 mg of calcium (see page 10, line 5). In examples 2, 4, 5, and 6 of the FR '844 patent the following quantities are reported respectively: 1.250g of calcium carbonate (0.5g of calcium ion); 1.5g of calcium pidolate (0.2g of calcium ion); 2g of calcium pidolate (0.27g of calcium ion); and 1.250g of calcium carbonate (0.5g of calcium ion). Furthermore, in Examples 3, 8 and 9, 3.74g of calcium pidolate are present containing 0.5g of calcium ion and example 7 reports 2.72g of calcium pidolate containing 0.35g of calcium ion.

This is in sharp contrast to the present claimed invention that claims 1-2 g of elemental calcium. Further, only the carbonate, pidolate, and lactate calcium salts are disclosed, and only calcium carbonate is claimed (see claim 12). Conversely, the preferred elemental calcium in the present invention is calcium phosphate. Its insolubility necessitates use of specific binding agents. Since the calcium phosphate salt is not used in FR '844, there is no need to look for the specific binding agents of the present invention. The distinction between the different salts, amount of calcium present and the binders used is a very significant one, and is the one of the central reasons the present claimed invention

is not rendered obvious by the FR' 844 patent.

Claim 1 of FR '844 specifically requires the use of a dry and wet binder, the process comprising the formation of solutions and suspensions. On page 6, line 31, it is reported that the wet granulation of calcium carbonate is mixed with polyvinyl pyrrolidone (a solid) to obtain a humid mass which is dried on an air bed (see page 7, lines 8 and 9). Other solid binders (e.g. cellulose, maltodextrines, sweeteners) may be used. However, the binders of the present invention rely on the use of liquid binders and a homogenizing step. Therefore, the claimed compositions are not made obvious by the FR '844 patent.

The prior art reference cannot be easily modified to include the unique structural and functional advantages described in the present invention. The present claimed invention results in an easily manufactured homogeneous combination of Vitamin D and calcium in a particular ratio that is palatable and encourages patient compliance. These elements of the present invention are neither disclosed nor addressed by the prior art.

It is apparent from the foregoing that it is insufficient to have a simple combination of Vitamin D and calcium in a pharmaceutical formulation. It is the unique ratio of Vitamin D and calcium together with propylene glycol, polyethylene glycol, liquid paraffin or silicone oil binders that result in significant advantages over the prior art. The present invention provides homogeneous distribution low dosages of Vitamin D with high dosages of calcium that is stable, bioavailable, palatable and suitable for high-speed production machines. Additionally, the present formulation overcomes problems due to "granulation" of the calcium salt. The glycol diffuses over the calcium granules, resulting in a binding effect over the small granules of coated Vitamin D_3, resulting in a mixture having flow characteristics conducive to processing by high output machines and actually facilitates subsequent reconstitution of a dispersion. It is urged that the unique structural and functional composition of the

present application is unobvious. Given the aforementioned distinctions, it is maintained that the prior art references do not teach or suggest the present invention.

Since the prior art of record fails to make the claimed subject matter obvious, each ground of rejection should be reversed and patent protection allowed to the inventor's unobvious contribution to the art.

Respectfully submitted,

James V. Costigan
Registration No.: 25, 669

MAILING ADDRESS
Hedman & Costigan, P.C.
1185 Avenue of the Americas
New York, NY 10036
(212) 302-8989

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(9) Appendix - Claims on Appeal

1. A pharmaceutical composition containing as active principles Vitamin D and a calcium salt which comprises a binding agent selected from the group consisting of propylene glycol, a polyethylene glycol of molecular weight between 300 and 1500, liquid paraffin and silicone oil, said Vitamin D being present in an amount of 500-1000 I.U. of Vitamin D and said calcium salt being present in a ratio of 1- 2 g of calcium, calculated as elemental calcium, for each 500-1000 I.U. of Vitamin D.

2. A pharmaceutical composition according to Claim 1, in which the calcium used is in the form of a salt selected from the group consisting of phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate and chloride.

3. Pharmaceutical composition according to Claim 1, in which the calcium salt is calcium phosphate.

4. Pharmaceutical composition according to Claim 3, wherein the calcium phosphate is 30-80% by weight calculated on the total composition.

5. Pharmaceutical composition according to Claim 1, in which the Vitamin D used is Vitamin D_2 (or ergocalciferol), Vitamin D_3 (or cholecalciferol), or one of their mixtures.

6. Pharmaceutical composition according to Claim 5, in which the vitamin used is Vitamin D_3.

7. A pharmaceutical composition in a sachet dosage form according to Claim 1, containing the propylene glycol in a quantity comprised between 5-15% by weight calculated on the total composition.

8. A pharmaceutical tablet according to Claim 1, containing liquid paraffin or silicone oil.

13. A process for the preparation of a pharmaceutical composition according to Claim 1, characterized by the following steps:
a) In a granulator turning at high speed, distributing a binding agent, consisting of propylene glycol or low molecular-weight polyethylene glycols over a calcium salt;
b) Adding colloidal silica, approximately 25% of mannite, citric acid, and sodium saccharin, and mixing for an appropriate time and at an appropriate speed to produce a first mixture;
c) Adding a second mixture, prepared separately, consisting of sucrose palmitate, a suspending agent, flavoring, a coloring agent, approximately 75% of the mannite and the Vitamin D_3, and mixing together with the first mixture to form a granulate; and
d) Distributing the granulate thus obtained into sachets.

14. A process for the preparation of a pharmaceutical composition according to Claim 1, characterized by the following steps:
a) In a granulator turning at high speed, placing a binding agent, consisting of liquid paraffin or silicon oil, over a calcium salt;
b) Adding in order, to a mixture of colloidal silica, carboxymethyl cellulose and sodium saccharin previously sifted, the Vitamin D_3 and sorbitol, mixing thoroughly every time before a new ingredient is added, and pouring the mixture into the rotating granulator and mixing for an appropriate time and at an appropriate speed to form a granulate; and
c) Compressing the granulate to a required weight to obtain tablets.

15. Composition According to Claim 1, for use in the treatment of nutritional deficiency of calcium and Vitamin D

in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures.

16. Composition According to Claim 1, for use in the prevention of osteoporosis induced by treatment with corticosteroids.

17. Method for treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures, in which therapeutically effective quantities of a composition according to Claim 1 are administered to the patient.

18. Method according to Claim 16 for the prevention of osteoporosis induced by treatment with corticosteroids.